GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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ALFONSO R GENNARO
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and Editor

ject insulin into their thigh may experience a precipitous drop in blood sugar that is not seen following injection into the arm or abdominal wall, since running markedly increases blood flow to the leg. Generally, the rate of absorption following injection of an aqueous preparation into the deltoid or vastus lateralis is faster than when the injection is made into the gluteus maximus. The rate is particularly slower for females after injection into the gluteus maximus. This has been attributed to the different distribution of subcutaneous fat in males and females, since fat is relatively poorly perfused. Very obese or emaciated patients may exhibit unusual patterns of absorption following intramuscular or subcutaneous injection. Very slow, constant absorption from the intramuscular site results if the drug is injected in solution in oil or suspended in various other repository vehicles. Penicillin often is administered in this manner. Substances too irritating to be injected subcutaneously may sometimes be given intramuscularly.

Intraarterial. Occasionally a drug is injected directly into an artery to localize its effect in a particular tissue or organ. However, this practice usually has dubious therapeutic value. Diagnostic agents are sometimes administered by this route. Intraarterial injection requires great care and should be reserved for experts. The first-pass and cleansing effects of the lung are not available when drugs are given by this route.

Intrathecal. The blood–brain barrier and the blood–cerebrospinal fluid barrier often preclude or slow the entrance of drugs into the CNS. Therefore, when local and rapid effects of drugs on the meninges or cerebrospinal axis are desired, as in spinal anesthesia or acute CNS infections, drugs are sometimes injected directly into the spinal subarachnoid space.

Intraperitoneal. The peritoneal cavity offers a large absorbing surface from which drugs enter the circulation rapidly, but primarily by way of the portal vein; first-pass hepatic losses are thus possible. Intraperitoneal injection is a common laboratory procedure, but it is seldom employed clinically. The dangers of producing infection and adhesions are too great to warrant the routine use of this route in human beings.

Pulmonary Absorption. Gaseous and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid by this route, because the surface area is large. The principles governing absorption and excretion of anesthetic and other therapeutic gases are discussed in Chapters 13, 14, and 16.

In addition, solutions of drugs can be atomized and the fine droplets in air (aerosol) inhaled. Advantages are the almost instantaneous absorption of a drug into the blood, avoidance of hepatic first-pass loss, and, in the case of pulmonary disease, local application of the drug at the desired site of action. For example, drugs can be given in this manner for the treatment of bronchial asthma (*see* Chapter 28). The main disadvantages are poor ability to regulate the dose, cumbersomeness of the methods of administration, and the fact that many gaseous and volatile drugs produce irritation of the pulmonary epithelium.

Pulmonary absorption is an important route of entry of certain drugs of abuse and of toxic environmental substances of varied composition and physical states (*see* Section XVII). Both local and systemic reactions to allergens may occur subsequent to inhalation.

Topical Application. ***Mucous Membranes.*** Drugs are applied to the mucous membranes of the conjunctiva, nasopharynx, oropharynx, vagina, colon, urethra, and urinary bladder primarily for their local effects. Occasionally, as in the application of antidiuretic hormone to the nasal mucosa, systemic absorption is the goal. Absorption through mucous membranes occurs readily. In fact, local anesthetics applied for local effect sometimes may be absorbed so rapidly that they produce systemic toxicity.

Skin. Few drugs readily penetrate the intact skin. Absorption of those that do is proportional to the surface area over which they are applied and to their lipid solubility, since the epidermis behaves as a lipid barrier (*see* Chapter 64). The dermis, however, is freely permeable to many solutes; consequently, systemic absorption of drugs occurs much more readily through abraded, burned, or denuded skin. Inflammation and other conditions that increase cutaneous blood flow also enhance absorption. Toxic effects sometimes are produced by absorption through the skin of highly lipid-soluble substances (*e.g.*, a lipid-soluble insecticide in an organic solvent). Absorption through the skin can be enhanced by suspending the drug in an oily vehicle and rubbing the resulting preparation into the skin. This method of administration is known as *inunction*. Because hydrated skin is more permeable than dry skin, the dosage form may be modified or an occlusive dressing may be used to facilitate absorption. Controlled-release topical patches are recent innovations. A patch containing scopolamine, placed behind the ear where body temperature and blood flow enhance absorption, releases sufficient drug to the systemic circulation to protect the wearer from motion sickness. Transdermal estrogen replacement therapy yields low maintenance levels of estradiol while minimizing the high estrone metabolite levels observed following oral administration.

Eye. Topically applied ophthalmic drugs are used primarily for their local effects (*see* Chapter 65). Systemic absorption that results from drainage through the nasolacrimal canal is usually undesirable. In addition, drug that is absorbed after such drainage is not subject to first-pass hepatic elimination. Unwanted systemic pharmacological effects may occur for this reason when β-adrenergic antagonists are administered as ophthalmic drops. Local effects usually require absorption of the drug through the cornea; corneal infection or trauma may thus result in more rapid absorption. Ophthalmic delivery systems that provide prolonged duration of action (*e.g.*, suspensions and ointments) are useful additions to ophthalmic therapy. Ocular inserts, developed more recently, provide continuous delivery of low amounts of drug. Very little is lost through drainage; hence, systemic side effects are minimized.

Bioequivalence. Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions. In the past, dosage forms of a drug from different manufacturers and even different lots of preparations from a single manufacturer sometimes differed in their bioavailability. Such differences were seen primarily among oral dosage forms of poorly soluble, slowly absorbed drugs. They result from differences in crystal form, particle size, or other physical characteristics of the drug that are not rigidly controlled in formulation

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bility, and energy from an active transport system enables the drug to penetrate the energy barrier *imposed by the lipids*. Actually, the lipids are not an important energy barrier; rather, the barrier is the force of attraction of the solvent water for its dipolar-to-polar solute, so that it is difficult for the solute to leave the water and enter the lipid.

Drugs with a high solubility in the membrane lipids pass easily through the membrane. Even when their dimensions are small enough to permit passage through pores, lipid-soluble drugs primarily pass through the membrane lipids, not only because chemical partition favors the lipid phase but also because the surface area occupied by pores is only a small fraction of the total membrane area.

LIPID SOLUBILITY AND PARTITION COEFFICIENTS—As early as 1902, Overton investigated the importance of lipid solubility to the penetration and absorption of drugs. Eventually, it was recognized that more important than lipid solubility was the lipid-water distribution coefficient; ie, a high lipid solubility does not favor penetration unless the water solubility is low enough so that the drug is not entrained in the aqueous phase.

In Figure 57-11 is illustrated the relationship between the chloroform-water partition coefficient and the colonic absorption of barbiturates. Chloroform probably is not the optimal lipid solvent for such a study, and natural lipids from nerve or other tissues have been shown to be superior in the few instances in which they have been employed. Nevertheless, the correlation shown in the figure is a convincing one.

When the water solubility of a substance is so low that a significant concentration in water or extracellular fluid cannot be achieved, absorption may be negligible in spite of a favorable partition coefficient. Hence, mineral oil, petrolatum, etc, virtually are unabsorbed. The optimal partition coefficient for permeation of the skin appears to be lower than that for the permeation of the cell membrane, perhaps being as low as one.

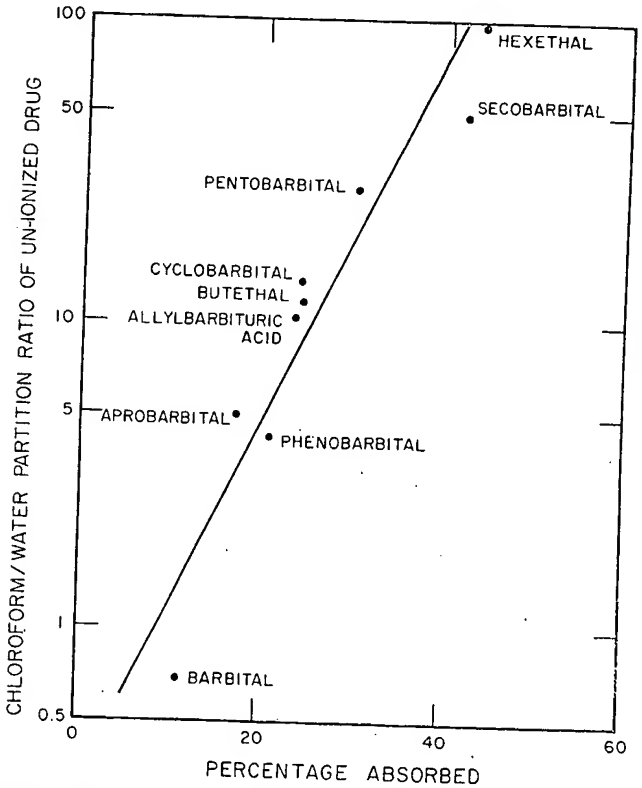

Figure 57-11. The relationship of absorption of the un-ionized forms of drugs from the colon of the rat to the chloroform:water partition coefficient (courtesy, Schanker[6]).

DIPOLARITY, POLARITY, AND NONIONIC DIFFUSION—The partition coefficient of a drug depends upon the polarity and the size of the molecule. Drugs with a high dipole moment, even though un-ionized, have a low lipid solubility and, hence, penetrate poorly. An example of a highly dipolar substance with a low partition coefficient, which does not penetrate into cells, is sulfisoxazole. Sulfadiazine is somewhat less dipolar, has a chloroform-water partition coefficient 10 times that of sulfisoxazole, and readily penetrates cells. Ionization not only diminishes lipid solubility greatly but also may impede passage through charged membranes (see *Ionic Diffusion*, page 1111).

It often is stated that ionized molecules do not penetrate membranes, except for ions of small diameter. This is not necessarily true, because of the presence of membrane carriers for some ions, which effectively may shield or neutralize the charge (ion-pair formation). The renal tubular transport systems, which transport such obligate ions as tetraethylammonium, probably form ion-pairs. Furthermore, if an ionized molecule has a large nonpolar moiety such that an appreciable lipid solubility is imparted to the molecule in spite of the charge, the drug may penetrate, although usually at a slow rate. For example, various morphinan derivatives are absorbed passively from the stomach even though they are ionized completely at the pH of gastric fluid. Nevertheless, when a drug is a weak acid or base, the un-ionized form, with a favorable partition coefficient, passes through a biological membrane so much more readily than the ionized form that for all practical purposes, only the un-ionized form is said to pass through the membrane. This has become known as the *principle of nonionic diffusion*.

This principle is the reason that only the concentrations of the un-ionized form of the barbiturates are plotted in Figure 57-11.

For the purpose of further illustrating the principle, Table 57-1 is provided.[7] In the table, the permeability constants for penetration into the cerebral spinal fluid of rats are higher for un-ionized drugs than for ionized ones. The apparent exceptions—barbital, sulfaguanidine, and acetylaminoantipyrine—may be explained by the dipolarity of the un-ionized molecules. With barbital, the two lipophilic ethyl groups are too small to compensate for the considerable dipolarity of the un-ionized barbituric acid ring; also it may be seen that barbital is appreciably ionized, which contributes to the relatively small permeability constant. Sulfaguanidine and acetylaminoantipyrine are both very polar molecules. Mecamylamine also might be considered an exception, since it shows a modest permeability even though strongly ionized; there is no dipolarity in mecamylamine except in the amino group.

Absorption of Drugs

Absorption is the process of movement of a drug from the site of application into the extracellular compartment of the body. Inasmuch as there is a great similarity among the various membranes that a drug may pass through to gain access to the extracellular fluid, it might be expected that the particular site of application (or *route*) would make little difference to the successful absorption of the drug. In actual fact, it makes a great deal of difference; many factors, other than the structure and composition of the membrane, determine the ease with which a drug is absorbed. These factors are discussed in the following sections, along with an account of the ways that drug formulations may be manipulated to alter the ability of a drug to be absorbed readily.

ROUTES OF ADMINISTRATION

Drugs may be administered by many different routes. The various routes include oral, rectal, sublingual or buccal, paren-

Table 57-1. Rates of Entry of Drugs in CSF and the Degrees of Ionization of Drugs at pH 7.4[7]

DRUG/CHEMICAL	% BINDING TO PLASMA PROTEIN	pK_a[a]	% UN-IONIZED AT pH 7.4	PERMEABILITY CONSTANT ($P\ min^{-1}$) ± S.E.
Drugs mainly ionized at pH 7.4				
5-Sulfosalicylic acid	22	(strong)	0	<0.0001
N-Methylnicotinamide	<10	(strong)	0	0.0005 ± 0.00006
5-Nitrosalicylic acid	42	2.3	0.001	0.001 ± 0.0001
Salicylic acid	40	3.0	0.004	0.006 ± 0.0004
Mecamylamine	20	11.2	0.016	0.021 ± 0.0016
Quinine	76	8.4	9.09	0.078 ± 0.0061
Drugs mainly un-ionized at pH 7.4				
Barbital	<2	7.5	55.7	0.026 ± 0.0022
Thiopental	75	7.6	61.3	0.50 ± 0.051
Pentobarbital	40	8.1	83.4	0.17 ± 0.014
Aminopyrine	20	5.0	99.6	0.25 ± 0.020
Aniline	15	4.6	99.8	0.40 ± 0.042
Sulfaguanidine	6	>10.0[b]	>99.8	0.003 ± 0.0002
Antipyrine	8	1.4	>99.9	0.12 ± 0.013
N-Acetyl-4-aminoantipyrine	<3	0.5	>99.9	0.012 ± 0.0010

[a] The dissociation constant of both acids and bases is expressed as the pK_a, the negative logarithm of the acidic dissociation constant.
[b] Sulfaguanidine has a very weakly acidic group (pK_a > 10) and two very weakly basic groups (pK_a 2.75 and 0.5). Consequently, the compound is almost completely undissociated at pH 7.4.

teral, inhalation, and topical. The choice of a route depends upon both convenience and necessity.

ORAL ROUTE—This is obviously the most convenient route for access to the systemic circulation, providing that various factors do not militate against this route. Oral administration does not always give rise to sufficiently high plasma concentrations to be effective; some drugs are absorbed unpredictably or erratically; patients occasionally have an absorption malfunction. Drugs may not be given by mouth to patients with GI intolerance or who are in preparation for anesthesia or who have had GI surgery. Oral administration also is precluded in coma.

RECTAL ROUTE—Drugs that ordinarily are administered by the oral route usually can be administered by injection or by the alternative *lower enteral* route, through the anal portal into the rectum or lower intestine. With regard to the latter, *rectal suppositories* or *retention enemas* formerly were used quite frequently, but their popularity has abated somewhat, owing to improvements in parenteral preparations. Nevertheless, they continue to be valid and, sometimes, very important ways of administering a drug, especially in pediatrics and geriatrics. In Figure 57-12[8] the availability of a drug by retention enema may be compared with that by the intravenous and oral routes and rectal suppository administration. It is apparent that the retention enema may be a very satisfactory means of administration but that rectal suppositories may be inadequate when rapid absorption and high plasma levels are required. The illustration is not intended to lead the reader to the conclusion that a retention enema always will give more prompt and higher blood levels than the oral route, for converse findings for the same drug have been reported,[9] but rather to show that the retention enema may offer a useful substitute for the oral route.

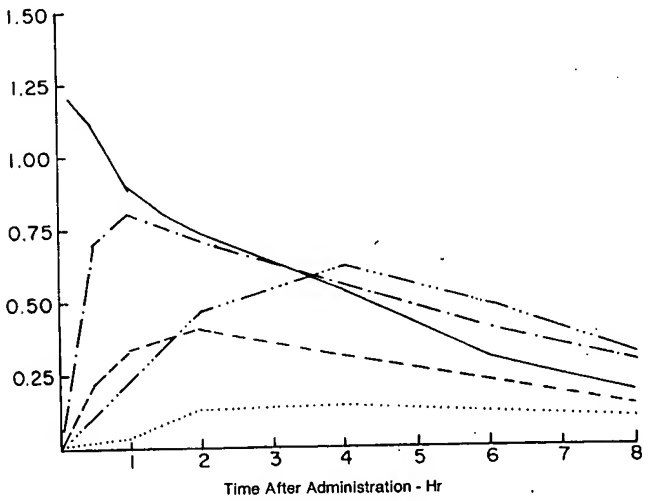

Figure 57-12. Blood concentration in mg/100 mL of theophylline (ordinate) following administration to humans of aminophylline in the amounts and by the routes indicated. Doses: per 70 kg. Theophylline-ethylenediamine by various routes: —— intravenous, 0.5 g; – · – · – retention enema, 0.5 g; — ··· — ··· — oral tablets-PI, 0.5 g; - - - oral tablets-PI, 0.3 g; ···· rectal suppository, 0.5 g (courtesy, Truitt, *et al*,[8] adapted).

SUBLINGUAL OR BUCCAL ROUTE—Even though an adequate plasma concentration eventually may be achievable by the oral route, it may rise much too slowly for use in some situations when a rapid response is desired. In such situations parenteral therapy usually is indicated. However, the patients with angina pectoris may get quite prompt relief from an acute attack by the *sublingual* or *buccal* administration of nitroglycerin, so that parenteral administration may be avoided. When only small amounts of drugs are required to gain access to the blood, the buccal route may be very satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route.

PARENTERAL ROUTES—These routes, by definition, include any route other than the oral-GI (enteral) tract, but in common medical usage the term excludes topical administration and includes only various hypodermic routes. Parenteral administration includes the intravenous, intramuscular, and subcutaneous routes. Parenteral routes may be employed whenever enteral routes are contraindicated (see above) or inadequate.

The *intravenous* route may be preferred on occasion, even when a drug may be well absorbed by the oral route. There is no delay imposed by absorption before the administered drug reaches the circulation, and blood levels rise virtually as rapidly as the time necessary to empty the syringe or infusion bottle. Consequently, the intravenous route is the preferred route when an emergency calls for an immediate response.

In addition to the rapid rise in plasma concentration of drug, another advantage of intravenous administration is the greater predictability of the peak plasma concentration, which, with some drugs, can be calculated with a fair degree of precision. Smaller doses generally are required by the intravenous than by other routes, but this usually affords no advantage, inas-

much as the sterile injectable dosage form costs more than enteric preparations, and the requirements for medical or paramedical supervision of administration also may add to the cost and inconvenience.

Because of the rapidity with which drug enters the circulation, dangerous side effects to the drug may occur, which are often not extant by other routes. The principal untoward effect is a depression of cardiovascular function, which is often called *drug shock*. Consequently, some drugs must be given quite slowly to avoid vasculotoxic concentrations of drug in the plasma. Acute, serious, allergic responses also are more likely to occur by the intravenous route than by other routes.

Many drugs are too irritant to be given by the oral, intramuscular, or subcutaneous route and must, of necessity, be given intravenously. However, such drugs also may cause damage to the veins (phlebitis) or, if extravasated, cause necrosis (slough) around the injection site. Consequently, such irritant drugs may be diluted in isotonic solutions of saline, dextrose, or other media and given by slow infusion, providing that the slower rate of delivery does not negate the purpose of the administration in emergency situations.

Absorption by the *intramuscular route* is relatively fast, and this parenteral route may be used when an immediate effect is not required but a prompt effect is desirable. Intramuscular deposition also may be made of certain repository preparations, rapid absorption not being desired. Absorption from an intramuscular depot is more predictable and uniform than from a subcutaneous site.

Irritation around the injection site is a frequent accompaniment of intramuscular injection, depending upon the drug and other ingredients. Because of the dangers of accidental intravenous injection, medical supervision generally is required. Sterilization is necessary.

In *subcutaneous* administration the drug is injected into the alveolar connective tissue just below the skin. Absorption is slower than by the intramuscular route but, nevertheless, may be prompt with many drugs. Often, however, absorption by this route may be no faster than by the oral route. Therefore, when a fairly prompt response is desired with some drugs, the subcutaneous route may not offer much advantage over the oral route, unless for some reason the drug cannot be given orally.

The slower rate of absorption by the subcutaneous route is usually the reason why the route is chosen, and the drugs given by this route are usually those in which it is desired to spread the action out over a number of hours, to avoid either too intense a response, too short a response, or frequent injections. Examples of drugs given by this route are insulin and sodium heparin, neither of which is absorbed orally, and both of which should be absorbed slowly over many hours. In the treatment of asthma, epinephrine usually is given subcutaneously to avoid the dangers of rapid absorption and consequent dangerous cardiovascular effects. Many repository preparations, including tablets or pellets, are given subcutaneously. As with other parenteral routes, irritation may occur. Sterile preparations also are required. However, medical supervision is not required always and self-administration by this route is customary with certain drugs, such as insulin.

Intradermal injection, in which the drug is injected into, rather than below, the dermis, is rarely employed, except in certain diagnostic and test procedures, such as screening for allergic or local irritant responses.

Occasionally, even by the intravenous route, it is not possible, practical, or safe to achieve plasma concentrations high enough so that an adequate amount of drug penetrates into special compartments, such as the cerebrospinal fluid, or various cavities, such as the pleural cavity. The brain is especially difficult to penetrate with water-soluble drugs. The name *blood-brain barrier* is applied to the impediment to penetration. When drugs do penetrate, the choroid plexus often secretes them back into the blood very rapidly, so that adequate levels of drugs in the cerebrospinal fluid may be difficult to achieve. Consequently, *intrathecal* or *intraventricular* administration may be indicated.

Body cavities such as the pleural cavity normally are wetted by a small amount of effusate that is in diffusion equilibrium with the blood and, hence, is accessible to drugs. However, infections and inflammations may cause the cavity to fill with serofibrinous exudate that is too large to be in rapid diffusion equilibrium with the blood. *Intracavitary* administration, thus, may be required. It is extremely important that sterile, nonirritating preparations be used for intrathecal or intracavitary administration.

INHALATION ROUTE—Inhalation may be employed for delivering gaseous or volatile substances into the systemic circulation, as with most general anesthetics. Absorption is virtually as rapid as the drug can be delivered into the alveoli of the lungs, since the alveolar and vascular epithelial membranes are quite permeable, blood flow is abundant, and there is a very large surface for absorption.

Aerosols of nonvolatile substances also may be administered by inhalation, but the route is used infrequently for delivery into the systemic circulation because of various factors that contribute to erratic or difficult-to-achieve blood levels. Whether or not an aerosol reaches and is retained in pulmonary alveoli depends critically upon particle size. Particles larger than 1 μm in diameter tend to settle in the bronchioles and bronchi, whereas particles smaller than 0.5 μm fail to settle and mainly are exhaled. Aerosols are employed mostly when the purpose of administration is an action of the drug upon the respiratory tract itself. An example of a drug commonly given as an aerosol is isoproterenol, which is employed to relax the bronchioles during an asthma attack.

TOPICAL ROUTE—Topical administration is employed to deliver a drug at, or immediately beneath, the point of application. Although occasionally enough drug is absorbed into the systemic circulation to cause systemic effects, absorption is too erratic for the topical route to be used routinely for systemic therapy. However, various transdermal preparations of nitroglycerin and clonidine are employed quite successfully for systemic use. Some investigations with aprotic solvent vehicles such as dimethyl sulfoxide (DMSO) also have generated interest in topical administration for systemic effects. A large number of topical medicaments are applied to the skin, although topical drugs are also applied to the eye, nose, throat, ear, vagina, etc.

In man, percutaneous absorption probably occurs mainly from the surface. Absorption through the hair follicles occurs, but the follicles in man occupy too small a portion of the total integument to be of primary importance. Absorption through sweat and sebaceous glands generally appears to be minor. When the medicament is rubbed on vigorously, the amount of the preparation that is forced into the hair follicles and glands is increased. Rubbing also forces some material through the stratum corneum without molecular dispersion and diffusion through the barrier. Rather large particles of substances such as sulfur have been demonstrated to pass intact through the stratum corneum. When the skin is diseased or abraded, the cutaneous barrier may be disrupted or defective, so that percutaneous absorption may be increased. Since much of a drug that is absorbed through the epidermis diffuses into the circulation without reaching a high concentration in some portions of the dermis, systemic administration may be preferred in lieu of, or in addition to, topical administration.

FACTORS THAT AFFECT ABSORPTION

In addition to the physicochemical properties of drug molecules and biological membranes, various factors affect the rate of absorption and determine, in part, the choice of route of administration.